smaller pieces of DNA via recombination, or as modulators of gene expression through methylation of *cis*-acting transcriptional regulatory elements. Like some other infamous mucosal pathogens (*H. influenzae and Neisseria spp*), *H. pylori* uses slipped-strand mispairing to spur its adaptive evolution within its host niche: the resulting frame-shift mutations act as switches to turn production of proteins on or off. There is extensive discussion of how variation in gene content in the organism's *cag* pathogenicity island (and the PAI's type IV secretion system) are intimately linked to host responses.

The editors note in their preface that they wanted to create a book that "would summarize and review the accumulated knowledge on this important human pathogen." They have succeeded. In 2004, exactly twenty years will have elapsed since the "big gulp." The chances of making major advances in our understanding the biology of this microorganism and the determinants of its host relationships could not be brighter. DNA microarrays containing more than 98% of the known ORFs of the two sequenced strains are now available for whole genome genotyping of clinical isolates (Salama et al., Proc. Natl. Acad. Sci. USA *97*, 14668–14673, 2000). Undertaking a comprehensive screen for the presence or absence of bacterial genes in strains taken from defined patient populations, or from individuals over the course of their infection, provides an opportunity to build a knowledge base for correlating microbial and host phenotypes with *H. pylori* genotypes. Genetically manipulatable and environmentally defined animal models are becoming available to model host traits thought to function as risk factors for development of severe pathology. Methods are emerging for monitoring bacterial gene expression in vivo (Rokbi et al., Infect. Immunol. *69*, 4759–4766, 2001), raising the hope that both host and microbial gene expression can be monitored simultaneously during the course of infection. The feasibility of conducting screens for essential *H. pylori* genes has been demonstrated (Chalker et al., J. Bacteriol. *183*, 1259–1268, 2001). The first reported large-scale prokaryotic protein-protein interaction map has been produced using information from the sequenced *H. pylori* genome and a version of the yeast two-hybrid system (Rain et al., Nature *409*, 211–215, 2001). Amidst all of this emerging technology, this book should serve as an invaluable guide for placing new results into the broadest possible context.

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Targeting HIV: Beyond Protease and Reverse Transcriptase Inhibitors

Antiretroviral Therapy
Edited by E.D.A. De Clercq
Washington, DC: ASM Press (2001). 359 pp. $99.95

Two decades ago, a report by the Centers for Disease Control and Prevention (CDC) of an unusual cluster of opportunistic infections and malignancies in male homosexuals heralded the onset of the AIDS epidemic. The subsequent identification of human immunodeficiency virus as the etiologic agent of AIDS led quickly to a search for agents capable of inhibiting viral replication and restoring immune function. Since the first report of successful pharmacologic impact on HIV-1 disease progression in 1987, fifteen drugs belonging to three separate classes (nucleoside reverse transcriptase inhibitors [NRTI's], non-nucleoside RT inhibitors [NNRTI's], and protease inhibitors [PI's]) have been approved for treatment of HIV-1 infection by the US Food and Drug Administration, and over a dozen more are currently in development. The use of these agents has dramatically changed the clinical course of HIV-1 infection for those fortunate enough to have access (Palella et al., N. Engl. J. Med. *338*, 853–860, 1998). At the same time, this rapidly evolving field and the need to keep abreast of new developments represents a growing challenge to clinicians and researcher alike.

Antiretroviral Therapy summarizes much of the progress that has been made in the development of antiretroviral therapeutic agents. Edited by Erik De Clercq, who also coauthored several of the chapters, this book offers a broad overview of each of the different classes of drugs currently available for inhibition of HIV and reviews progress toward the development of novel classes of anti-HIV-1 therapeutics. The major focus of the book is on the inhibitors themselves, rather than on their clinical use, so much so that a more accurate title might have been *Antiretroviral Agents*. Those seeking a discussion of the vexing questions of when to initiate therapy, when to change from one regimen to another, how to manage treatment-related toxicities, or under what circumstances treatment interruption might be warranted will find little discussion of those treatment-related topics in this edition. Readers will, however, find a thorough discussion of the agents themselves, written in highly readable style and containing helpful figures and tables. Unfortunately, given the rapid pace of antiretroviral drug development, much of the material is already seriously out of date. Despite a publication date of 2001, most of the references date from 1999 or before, which in the end is the most serious shortcoming of the book.

The chapters on reverse transcriptase inhibitors and protease inhibitors provide thorough summaries of these agents. Particularly helpful is the thorough discussion of pathways for phosphorylation and metabolism of the nucleoside and nucleotide analogs, which must be activated intracellularly to their triphosphate or diphosphate forms, respectively. Detailed discussions of the calculated approach to the development of new agents such as ABT-378 through structure/function analyses provide interesting insights into drug discovery from authors who were involved in these processes, but results of promising clinical studies that formed the basis for FDA approval are not discussed. Structural considerations are also prominent in the chapter on the non-nucleoside RT inhibitors (NNRTIs), which is illustrated by helpful figures showing the structural basis for interaction of these inhibitors with RT; the chapter on the protease inhibitors would have been strengthened by inclusion of similar figures. Chapters on the RT inhibitors and protease inhibitors would have been enhanced by a discussion of the toxicities of these agents, but

this area was largely omitted. For example, there is no discussion of mitochondrial toxicity in the chapter of nucleoside RT inhibitors, and only brief mention of lipodystrophy in the protease inhibitor chapter.

The chapters on alternative targets for HIV inhibition provide important reviews of new approaches, but are among the most seriously impacted by the apparent slow road to publication of this edition. The chapter on cellular receptors as targets for anti-HIV agents focuses primarily on inhibition of the chemokine receptor CXCR4 by the bicyclam AMD3100. The chemokine receptors CCR5 and CXCR4 serve as coreceptors for HIV, and considerable effort is being devoted to the development of chemokine receptor blockers. Unfortunately, clinical development of AMD3100 has been halted due to toxicities observed in phase I clinical trials. The chapter could have been expanded to encompass inhibitors such as T-20 that interact with the transmembrane subunit of HIV-1 envelope (gp41) to prevent fusion of the viral and cell membranes (Kilby et al., Nat. Med. *4*, 1302–1307, 1998). The chapter on integrase inhibitors focuses almost entirely on nonspecific inhibitors whose mechanism of action depends on binding to DNA. Most of these compounds are not serious candidates for clinical development. The recent ground-breaking work of Hazuda and colleagues on the identification of compounds that specifically inhibit the integrase-mediated strand transfer reaction is not discussed (Hazuda et al., Science *287*, 646–650, 2000).

Agents that target the transcriptional regulation of HIV-1 are covered in two chapters, one that focuses on inhibitors of Tat and Rev, and another that focuses on cellular proteins involved in HIV-1 gene expression. Although both chapters have excellent discussions of the regulatory pathways that govern HIV-1 transcription and translation, there is considerable overlap. Surprisingly, attempts to inhibit HIV expression through gene therapies that direct overexpression of Tat-binding sequences (TAR decoy) or trans-dominant Rev mutants (RevM10) are not discussed (Bevec et al., Proc. Natl. Acad. Sci. USA *89*, 9870–9874, 1992; Sullenger et al., Cell *63*, 601–608, 1990). Equally surprising is the omission of ribozymes from the chapter on oligonucleotides as HIV-1 inhibitors. In fact, gene therapy and stem cell transplantation as possible approaches to the treatment of HIV infection are not addressed at all.

One of the newest areas of interest related to antiretroviral therapy is the use of these agents alone or in combination with other interventions to augment immune responses to HIV. This topic is dealt with in part in a chapter on therapeutic vaccines, which provides a review of the field up through 1998. However, a wealth of recent information providing strong rationale for therapeutic immunization is not cited, again apparently because of a long delay from the time the chapters were written until the book was published. Discussions of the impact of early treatment on immune responses (Oxenius et al., Proc. Natl. Acad. Sci. USA *97*, 3382–3387, 2000; Rosenberg et al., Science *278*, 1447–1450, 1997), the ability of a protease inhibitor, HAART, to promote production of new naive cells (Autran et al., Science *277*, 112–116, 1997), and the effect of treatment interruption on immunologic boosting in acute and chronic infection are not included. Moreover, readers will have to go to other sources to read about many approaches to therapeutic immunization that are now nearing or in clinical trials, such as the use of DNA vaccines, canarypox vectors, and antigen-pulsed dendritic cells.

The final chapters in the book focus on drug resistance, drug-drug interactions, and combination therapy. The chapter on emergence of drug-resistant HIV-1 includes a scholarly discussion of recently identified mechanisms of zidovudine resistance, although it overlaps significantly with the chapter on drug resistance testing. Both chapters include a table of important drug resistance mutations, but a number of discordances can be found. A cumbersome aspect of ASM style comes to the fore in these chapters as well. Abstracts are cited in the text, rather than with published references at the end of the chapter. Because so much of the work cited is available only in abstract form, on many pages whole paragraphs are taken up by these citations. Moreover, in 2001, one is left questioning why the main evidence in support of some major statements made derives from abstracts dated 1998 and earlier. The chapter on combination therapy provides a detailed review of the major clinical trials on which the current approach to antiretroviral therapy is based, but once again there are important treatment issues not discussed, particularly the toxicities associated with this therapy. The brief chapter on drug-drug interactions has an excellent table of the most significant interactions associated with drugs used in the treatment of HIV infection and its complications. However, the use of ritonavir to enhance the pharmacokinetic profile of other protease inhibitors, which has become a mainstay of current treatment strategies, is discussed in only three short paragraphs.

In summary, this book provides solid background information for those seeking an introduction to HIV inhibitors, but interested readers will have to search elsewhere to fill in the considerable gaps and to obtain information on the current state of the art. In an age in which plenary sessions of international meetings are posted on the world-wide web and authoritative summaries of every AIDS conference are available almost instantly on the internet, traditional print media face a daunting challenge in providing up-to-date, relevant information in a timely manner.

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Of Course Sex Matters

Exploring the Biological Contributions to Human Health—Does Sex Matter?
Edited by Theresa Wizemann and Mary-Lou Pardue
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267 pp. $44.95

Several years ago, I gave a talk at an International Women's Day luncheon on the then newly discovered SRY